REMARKS

Status of the Subject Application and the Present Response

Claims 1-3, 5-13 and 15-44 are pending in the patent application. Claims 11-13 and 15-20 have been rejoined by the Examiner in the instant office action. Claims 21-44 have been previously withdrawn from examination by the Examiner as directed to non-elected inventions. Claims 1-3, 5-13 and 15-20 are under examination, with claims 1-3, 5-13 and 15-20 being rejected, and claims 5, 6, 15 and 16 being objected to.

In the instant response, Claims 1 and 11 are amended to clarify that the presence of an oxidized probe indicate the presence of the reactive oxygen species. It is noted that the amendment is made to prove clarity of the claim language, and that no new matter has been introduced.

Applicants present the following remarks and arguments to address the issues raised by the Examiner in the office action.

Finality of the instant office action

In making the instant office action final, the Examiner states that Applicants's amendment necessitated the new grounds of rejection. Applicants respectfully disagree. Specifically, the instant office action raised a new prior art rejection of pending claims over Medford et al. (USPN 5,846,959). On the other hand, the amendments to claims 1 and 11 introduced by Applicants in the response dated December 28, 2006 only narrow the scope of the claims by incorporating elements from their dependent claims. Other changes to the claims merely relate to formality or improving clarity of claim language. Therefore, those amendments certainly did not necessitate this new art based rejection. Evidently, this new art rejection could have been made in the previous office action dated September 1, 2006 which

is the first office action on the Request for Continued Examination filed by Applicants on June 9, 2006. Since Applicants were not previously given any opportunity to consider this rejection, the instant office action should not have been made final. Accordingly, Applicants request that the finality be withdrawn.

Objection to the specification

The Examiner maintains the objection to the specification on the ground that singlet oxygen belongs to the broader genus of reactive oxygen species, and that the reference in the specification to conversion of "singlet oxygen" into "reactive oxygen species" is therefore repugnant to the art-recognized definition of reactive oxygen species. Applicants reiterate their willingness to make appropriate amendments to the specification once an allowable subject matter is indicated by the Examiner.

Claim objections

Claims 5, 6, 15 and 16 were objected to as allegedly being improper dependent claims. Applicants cannot understand the Examiner's rationale underlying the claims objections. The base claims 1 and 11 each recite several reactive oxygen species. On the other hand, the dependent claims 5-6 and 15-16 each recite some but not all of the reactive oxygen species specified in the base claims. It is also noted that detection of different reactive oxygen species can utilize different probes. Therefore, these claims are proper dependent claims because they are narrower in scope than the claims from which they depend. Should the Examiner choose to maintain the objections, Applicants respectfully request clarification.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 1-3, 5-13 and 15-20 were rejected as allegedly being indefinite. Specifically, with respect to claim 1, the Examiner questions how "detecting a 'probe' in step(c) amounts to a method of detecting an 'immunological response." In response, Applicants note that step(c) of claim 1 does not merely recite "detecting a probe," as alleged by the Examiner. Rather, it specifies detection of an oxidized probe. As disclosed in the specification (e.g., page 23, lines 1-4; and page 24, lines 15-23), the chemical probe is used to detect an oxidation product of the administered probe, and oxidation of the administered probe is catalyzed by an antibody generated reactive oxygen species. In addition, the specification teaches that during an immune response, activation and differentiation of B cells leads to secretion of antigen-specific antibodies (e.g., page 26, lines 21-23). Therefore, if the administered probe becomes oxidized, it indicates the presence of one of the recited reactive oxygen species which in turn means there is a immunological response which generates the reactive oxygen species. Similarly, claim 11 also specifies the detection of an oxidized product of the administered probe. As taught in the specification, inflammation is associate with immune activation and immune responses (e.g., page 27, lines 12-19). The antibodies involved in or activated by an inflammatory response will generate the reactive oxygen species recited in the claims which would catalyze oxidation of the administered probe. For example, neutrophils, the predominant cell types involved in acute inflammation, are known to have antibodies on their surface (page 87, lines 9-14).

It is also noted that the specification provides specific examples of using a chemical probe for the detection of antibody

generated reactive oxygen species. For example, indigo carmine and a few other probes were employed to detect ozone generated by antibodies (see, e.g., page 84, lines 4-24; and page 86, line 3 to page 87, line 6). In addition, the specification also exemplifies detection of ozone production by neutrophils with a specific probe for ozone, indigo carmine (see, e.g., page 87, line 19 to page 88, line 10).

To further improve clarity of the claim language, Applicants have herein amended claims to make it clearer that detection of the oxidized probe indicates the presence of a reactive oxygen species. In light of the clarification and claim amendments noted above, Applicants submit there is no indefiniteness in the presently claimed invention. Withdrawn of the instant rejection is accordingly requested.

Rejection under 35 U.S.C. § 102

The Examiner maintains the rejection of Claims 1-3 and 5-10 as allegedly anticipated by Iribarren et al. (Arterioscler. Thromb. Vasc. Biol. 17:1171, 1997). In addition, the Examiner rejects claims 1-3, 5-13 and 15-20 as allegedly anticipated by Medford et al. As explained below, Applicants respectfully traversed these rejections because the Examiner's reasoning underlying these rejections is clearly incorrect.

The law of anticipation is well settled. To constitute anticipation, the claimed subject matter must be identically disclosed in a single prior art reference. *In re Arkley*, 172 USPQ 524 at 526 (CCPA 1972). There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the art. *Scripps Clinic & Res. Found. V. Genentech, Inc.*, 927 F.2d 1565, 18 USPQ 2d 101 (Fed. Cir. 1991). To overcome an anticipation rejection, "it is only

necessary for the patentee to show some tangible difference between the invention and the prior art." *Del Mar engineering Lab v. Physio-Tronics, Inc.*, 642 F.2d 1167, 1172 (9th Cir. 1981). Further, an anticipation rejection based on inherence, as is the instant rejection, must be supported by factual and technical grounds establishing that the inherent feature must flow as a necessary conclusion, not simply a possible conclusion, from the teaching of the cited art. *Ex parte Levy*, 17 USPQ 2d 1461, 1464 (Bd. Pat. App. & Int. 1990); *In re Oelrich*, 666 F.2d 578, 212 USPQ 323, 326 (CCPA 1981).

In the instant case, the cited references do not and could not anticipate the present claims. Independent Claims 1 and 11 are respectively directed to a method for detecting an immunological response or a method for detecting an inflammatory response via detecting a reactive oxygen species generated by antibodies. To anticipate these claims, the cited art must teach each and every element recited in the claims, e.g., administering to a mammal a chemical probe for a reactive oxygen species; then detecting in a sample from the mammal an oxidized product of the administered probe; and thereby detecting an immunological response or an inflammatory response which is indicated by the presence of a reactive oxygen species generated by antibodies. As detailed below, none of the cited references would meet such a requirement, expressly or inherently.

First, Iribaren et al. discusses potential risk factors for carotid atherosclerosis. The factors examined by the authors include, e.g., serum levels of certain serum antioxidant vitamins (e.g., carotenoids, retinol, and α-tocopherol), susceptibility of LDL to hemin-induced oxidation, and presence of autoantibodies against malondialdehyde-LDL (MDA-LDL). Noting that the paper discusses dietary intake of vitamins by subjects, the Examiner

asserts that this reference teaches administering a chemical probe for reactive oxygen species. The Examiner alleges that the vitamins disclosed in Iribarren et al. are inherently probes for the reactive oxygen species recited in the present claims. Citing the detection of serum authoantibodies against MDA-LDL in human subjects, the Examiner states that Iribaren et al. also teaches detecting an oxidized probe in a sample from a mammal. The Examiner then concludes that this reference anticipates claim 1 and dependent claims.

With due respect, Applicants note that, contrary to the Examiner's assertion, Iribaren et al. does not teach the administration of dietary vitamins and then detection of an oxidized product of the administered vitamin. Rather, the paper only discusses information on vitamin uptake by patients which was obtained by a questionnaire (page 1172, right column, last paragraph). As stated in the paper, the purpose is to assess whether vitamin uptake may be the cause of the observed correlation between atherosclerosis and the discussed risk factors, e.g., serum level of antioxidant vitamins. To this end, the authors performed a control study using only subjects who do not take vitamin supplements (see, e.g., Iribaren et al., page 1174, right column, last paragraph).

In addition, even assuming as the Examiner alleged that this reference teaches the administration of a probe for reactive oxygen (antioxidant vitamin), it does not teach or suggest detection of an oxidized product of the probe. Instead, Iribaren et al. discusses detection and quantitation of an autoantibody against malondialdehyde-LDL (MDA-LDL). This antibody certainly is not an oxidized product of the administered probe (vitamin). Further, as disclosed in Iribaren et al., the presence of the autoantibody merely indicate oxidative modification of LDL.

There is no significant correlation between such autoantibodies and atherosclerosis (see, e.g., page 1175, left column, last paragraph). The data certainly does not suggest any link between vitamin uptake and the presence of the autoantibody in the serum. Hence, it is readily apparent Iribaren et al. does not teach the methods recited in claim 1 and dependent claims therefrom.

With respect to Medford et al., the Examiner asserts that this reference describes a method for detecting an antibody response that comprises the steps as recited in the presently claimed invention. The Examiner took the view that Medford et al. describes a method for detecting an immune response by administering an antioxidant. The Examiner further asserted that the antioxidants described in Medford et al. are inherently probes for the reactive oxygen species recited in the present claims. As noted below, Applicants respectfully submit that the Examiner's interpretation of the teaching of Medford et al. is inaccurate, if not simply wrong.

Medford et al. relates to methods for treating and detecting disorders mediated by VCAM (Col. 4, lines 28-29). It discloses that VCAM expression is induced by both polyunsaturated fatty acids (PUFAs) and hydroperoxides of PUFAs (oxidized PUFAs) (Col. 3, lines 27-34). The relevant disclosures in Medford that were noted by the Examiner relate to <u>different</u> embodiments: e.g., administering an antioxidant (thereby modulating VCAM expression on cell surface) (Col. 4, lines 36-39); evaluating levels of oxidized PUFAs (to assess oxidative environment of a host and its likely susceptibility to VCAM mediated diseases)(Col. 4, lines 28-35); and <u>administering PUFA or oxidized PUFA</u> to induce atherosclerosis or inflammatory diseases (as animal models of the diseases).

Contrary to the present claims, the various embodiments in

Medford et al. as quoted by the Examiner does not teach or suggest a method of administering a (non-oxidized) probe and then detecting an oxidized product of the probe. Applicants respectfully note that the alleged anticipation is based on nothing other than the Examiner's own "synthesis" of the claimed method by extracting the recited claim elements out of their context from the different and unrelated embodiments of Medford et al. For example, the discussion of inflammatory response in Medford et al. relates to in vivo animal models which are produced by administering to a host PUFA or oxidized PUFAs (Col. 4, lines 48-54). On the other hand, the administration of a chemical probe as alleged by the Examiner (Col. 4, lines 36-39) relates to using antioxidants to assess their effect on expression levels of VCAM and other molecules (via inhibition of PUFA oxidation by the antioxidants). It is readily clear these are entirely different embodiments. Contrary to what the Examiner is asserting, no one can rationally pick an element or disclosed feature from each of these embodiments and then combine them to arrive at the claimed method.

In addition, the PUFA or oxidized PUFAs administered to create the animal models are not the chemical probe (antioxidants) used to analyze their effect on VCAM expression. Thus, if an antioxidant is the chemical probe in Medford et al., as alleged by the Examiner, there is no discussion of detection of an oxidized product of the chemical probe. Instead, Medford at most alluded to evaluation of serum levels of PUFA or oxidized PUFAs, not the level of oxidation product of an administered antioxidant. On the other hand, if PUFAs are the chemical probe to be used, Medford et al. does not disclose that only oxidized fatty acids should be detected as the Examiner apparently assumes. Rather, Medford et al. teaches that both non-oxidized

and oxidized PUFAs can induce VCAM expression (Col. 3, lines 27-30) and both non-oxidized and oxidized PUFAs can be used to detect VCAM expression (Col. 4, lines 41-43). Nothing in this reference teaches or even suggests that one should administer a non-oxidized PUFA to a mammal and then detect only oxidized product of that PUFA. Therefore, just like Iribaren et al., Medford et al. also cannot anticipate the presently rejected claims.

More importantly, the cited references do not teach or suggest that antibodies have a catalytic role in generating reactive oxygen species. They certainly do not disclose that reactive oxygen species such as ozone and hydrogen peroxide can be generated by any endogenous protein, let alone the use of a chemical probe to detect the presence of an reactive oxygen species generated by antibodies. For Medford et al, one would merely gather from its disclosure that both oxidized and non-oxidized PUFAs can induce VCAM expression and such expression is somehow linked to certain disorders. Iribaren et al. at most would teaches a skilled artisan that serum levels of certain antioxidant vitamins are associated with atherosclerosis. Such disclosures are definitely not sufficient, if not completely irrelevant, for establishing the required "factual and technical grounds" for an inherent anticipation of the claimed invention. The cited references certainly do not provide teachings from which the presently claimed invention can flow as a necessary conclusion.

Finally, Applicants wish to remind the Examiner that no reasoning was provided in the office action as to why the cited references can anticipate claims that depend from independent claims 1 and 11. For example, the cited art certainly do not disclose the use of probes for detecting all the specific

reactive oxygen species recited in the claims, e.g., ozone. The cited reference also do not teach use of the specific chemical probes set forth in the dependent claims, e.g., indigo carmine. Clarification from the Examiner on the rejection of these dependent claims is strongly urged.

For all the reasons state above, Applicants submit that the cited reference could not anticipate the presently claimed invention. Withdrawal of the instant rejections are therefore respectfully requested.

CONCLUSION

In view of the foregoing, Applicant believes all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If a telephone conference would expedite prosecution of this application, please telephone the undersigned attorney at 858-784-2937. If there are any additional fees (or overpayments) associated with this Response, or any Response associated with this application, the Director is hereby authorized to charge (or credit) our Deposit Account No. 19-0962.

Respectfully submitted,

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Date

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